

FORM PTO-1390  
(REV 1-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

WC131

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

09/269903

INTERNATIONAL APPLICATION NO.

PCT/GB97/02726

INTERNATIONAL FILING DATE

06 October 1997

PRIORITY DATE CLAIMED

04 October 1996

TITLE OF INVENTION

Colonic Delivery of Weak Acid Drugs

APPLICANT(S) FOR DO/EO/US

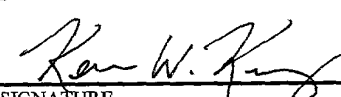
WATTS, Peter James

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (unexecuted)
10. ☐ A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.  
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: Copy of published application

U.S. APPLICATION NO (if known, see 37 CFR 1.5)		INTERNATIONAL APPLICATION NO <b>PCT/GB97/02726</b>		ATTORNEY'S DOCKET NUMBER <b>WC131</b>	
<b>17. <input checked="" type="checkbox"/> The following fees are submitted:</b> <b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$ 970.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... 840.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... 760.00  International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... 670.00  International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... 96.00  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				CALCULATIONS PTO USE ONLY	
				\$ 840.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$ 130.00	
<b>CLAIMS</b>	<b>NUMBER FILED</b>	<b>NUMBER EXTRA</b>	<b>RATE</b>	<b>\$</b>	
Total claims	20 - 20 =		x \$18.00	\$	
Independent claims	4 - 3 =		x \$78.00	\$ 78.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$260.00	\$	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$ 1,048.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				+	
<b>SUBTOTAL =</b>				\$ 1,048.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	
<b>TOTAL NATIONAL FEE =</b>				\$ 1,048.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				+	
<b>TOTAL FEES ENCLOSED =</b>				\$ 1,048.00	
				Amount to be refunded:	\$
				charged:	\$
<p>a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>1,048.00</u> to cover the above fees is enclosed.</p> <p>b. <input type="checkbox"/> Please charge my Deposit Account No. <u>01-2507</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>01-2507</u>. A duplicate copy of this sheet is enclosed.</p>					
<p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.</p> <p>SEND ALL CORRESPONDENCE TO:</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 60%;"> <p>Patrea L. Pabst, Esq.            Arnall Golden &amp; Gregory, LLP            2800 One Atlantic Center            1201 West Peachtree Street            Atlanta, Georgia 30309-3450            United States of America</p> </div> <div style="width: 35%; text-align: right;"> <p>            SIGNATURE  <u>Kevin W. King</u>            NAME  <u>42,737</u>            REGISTRATION NUMBER</p> </div> </div>					

IN THE UNITED STATES RECEIVING OFFICE  
FOR THE PATENT COOPERATION TREATY

Applicant: Peter James Watts

International Application No.: PCT/GB97/02726  
International Filing Date: 6 October 1997

U.S. Serial No.:  
Filed: 02 April 1999

Express Mail Label No: EL273009964US  
Date of Deposit: 02 April 1999

For: COLONIC DELIVERY OF WEAK ACID DRUGS

Box PCT  
Assistant Commissioner for Patents  
Washington, D.C. 20231

**PRELIMINARY AMENDMENT**

Sir:

Please amend the application as follows.

**In the Specification**

At page 1, below the title, please insert:

--Priority is claimed under 35 U.S.C. § 119 to PCT/GB97/02726, filed October 6, 1997,  
which corresponds to GB 9620709.07 filed October 4, 1996.--.

At page 22, line 1, please delete "Claims" and insert --I claim:-- in place thereof.

**In the Claims**

1. (Amended) A controlled release composition [including] comprising pellets,  
wherein each pellet [comprising] comprises an inner core[, which core comprises, or is  
coated with,] comprising a drug[, which drug] which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

[which] wherein the inner core is [subsequently] coated with a rate-controlling membrane that determines drug release,

wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and

wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

2. (Amended) [A composition as claimed in Claim] The composition of claim 1 wherein the drug is a thromboxane synthase A<sub>2</sub> inhibitor or a thromboxane A<sub>2</sub>/prostaglandin endoperoxide receptor antagonist.

3. (Amended) [A composition as claimed in Claim] The composition of claim 2 wherein the drug is ridogrel.

4. (Amended) [A composition as claimed in any one of Claims 1 to 3,] The composition of claim 1 wherein the rate-controlling membrane comprises a material which forms a water-insoluble, but water-permeable layer and from which release of the drug is by diffusion through the layer.

5. (Amended) [A composition as claimed in Claim 4,] The composition of claim 4 wherein the rate-controlling membrane is formulated from a methacrylate copolymer or ethylcellulose.

6. (Amended) [A composition as claimed in Claim 5,] The composition of claim 5 wherein the rate-controlling membrane is formulated from [ethylcellulose or Eudragit] EUDRAGIT<sup>TM</sup> NE30D.

7. (Amended) [A composition as claimed in Claim 6 where] The composition of claim 5 wherein the rate-controlling membrane is ethylcellulose.

8. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the inner core is a sugar sphere.

9. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the salt is at least 10 times more soluble than the free acid form of the drug at pH 4.5 to 8.0 at 37 °C.

10. (Amended) [A composition as claimed in any Claim 9,] The composition of claim 9 wherein the salt is at least 100 times more soluble than the free acid form of the drug.

11. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the salt is an alkali metal salt.

12. (Amended) [A composition as claimed in Claim 11,] The composition of claim 11 wherein the alkali metal is sodium or potassium.

13. (Amended) [A composition as claimed in any one of the preceding claims] The composition of claim 1 wherein the pellets are administered in a starch capsule coated with a combination of polymethacrylates that is designed to disintegrate and release the pellets in the terminal ileum or in the colon.

14. (Amended) [A composition as claimed in any one of the preceding claims] The composition of claim 1 wherein the drug is used for [the] a treatment selected from the group consisting of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and inflammatory bowel disease.

15. (Amended) A [process] method for [the preparation of] making a composition [according to any one of the preceding claims which comprises] comprising pellets.

wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition, the method comprising

making a salt of the drug, and

coating [said] the salt onto the inner cores.

16. (Amended) [A process as claimed in Claim 15,] The method of claim 15 wherein the salt is prepared as part of a preparation process for the coating of the inner cores.

17. (Amended) A method of improving the controlled release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0, [which comprises administering a composition according any one of Claims 1 to 14 to a patient, preferably a human patient] the method comprising administering the drug in a composition comprising pellets, wherein each pellet comprises an inner core comprising the drug which possesses

(a) a free acid group which can be converted into an alkali metal salt and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition

is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

Please cancel claim 18.

19. (Amended) A method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and/or inflammatory bowel disease, [which method comprises] the method comprising

administering to a patient in need of treatment a composition [according to any one of Claims 1 to 14 to a patient, preferably a human patient] comprising pellets,  
wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

Please cancel claim 20.

Please add the following new claims.

21. (New) The composition of claim 1 wherein the pellets are compressed into tablets which are coated to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

22. (New) The composition of claim 1 wherein the core is between about 0.3 to 5 mm in size.

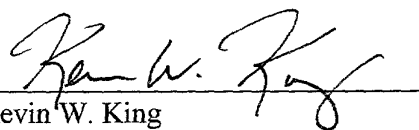
### Remarks

The specification has been amended to reference the priority application.

Claims 1-20, as shown in the published PCT application with amended sheets 22-24 attached to the response to second written opinion, are pending prior to entry of this Preliminary Amendment. Claims 18 and 20 have been canceled, and claims 1-17 and 19 have been amended to eliminate multiple dependencies, to use Markush groups where appropriate, and to clarify the claimed compositions and methods. New claims 21 and 22 have been added. Support for these claims is found at least on page 7, lines 2-4 and lines 11-13. No new matter has been added.

Allowance of claims 1-17, 19, 21, and 22 is earnestly solicited.

Respectfully submitted,



Kevin W. King  
Reg. No. 42,737

Date: 02 April 1999

ARNALL, GOLDEN & GREGORY, LLP  
2800 One Atlantic Center  
1201 West Peachtree Street  
Atlanta, Georgia 30309-3450  
(404) 873-8596  
(404) 873-8597

**APPENDIX**  
*Claims as Preliminarily Amended*

1. (Amended) A controlled release composition [including] comprising pellets, wherein each pellet [comprising] comprises an inner core[, which core comprises, or is coated with,] comprising a drug[, which drug] which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

[which] wherein the inner core is [subsequently] coated with a rate-controlling membrane that determines drug release,

wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and

wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

2. (Amended) [A composition as claimed in Claim] The composition of claim 1 wherein the drug is a thromboxane synthase A<sub>2</sub> inhibitor or a thromboxane A<sub>2</sub>/prostaglandin endoperoxide receptor antagonist.

3. (Amended) [A composition as claimed in Claim] The composition of claim 2 wherein the drug is ridogrel.

4. (Amended) [A composition as claimed in any one of Claims 1 to 3,] The composition of claim 1 wherein the rate-controlling membrane comprises a material which forms a water-insoluble, but water-permeable layer and from which release of the drug is by diffusion through the layer.

5. (Amended) [A composition as claimed in Claim 4,] The composition of claim 4 wherein the rate-controlling membrane is formulated from a methacrylate copolymer or ethylcellulose.

6. (Amended) [A composition as claimed in Claim 5,] The composition of claim 5 wherein the rate-controlling membrane is formulated from [ethylcellulose or Eudragit] EUDRAGIT<sup>TM</sup> NE30D.

7. (Amended) [A composition as claimed in Claim 6 where] The composition of claim 5 wherein the rate-controlling membrane is ethylcellulose.

8. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the inner core is a sugar sphere.

9. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the salt is at least 10 times more soluble than the free acid form of the drug at pH 4.5 to 8.0 at 37 °C.

10. (Amended) [A composition as claimed in any Claim 9,] The composition of claim 9 wherein the salt is at least 100 times more soluble than the free acid form of the drug.

11. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the salt is an alkali metal salt.

12. (Amended) [A composition as claimed in Claim 11,] The composition of claim 11 wherein the alkali metal is sodium or potassium.

13. (Amended) [A composition as claimed in any one of the preceding claims] The composition of claim 1 wherein the pellets are administered in a starch capsule coated with a combination of polymethacrylates that is designed to disintegrate and release the pellets in the terminal ileum or in the colon.

14. (Amended) [A composition as claimed in any one of the preceding claims] The composition of claim 1 wherein the drug is used for [the] a treatment selected from the group consisting of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and inflammatory bowel disease.

15. (Amended) A [process] method for [the preparation of] making a composition [according to any one of the preceding claims which comprises] comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition, the method comprising

making a salt of the drug, and

coating [said] the salt onto the inner cores.

16. (Amended) [A process as claimed in Claim 15,] The method of claim 15 wherein the salt is prepared as part of a preparation process for the coating of the inner cores.

17. (Amended) A method of improving the controlled release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0, [which comprises administering a composition according any one of Claims 1 to 14 to a patient, preferably a human patient] the method comprising administering the drug in a composition comprising pellets, wherein each pellet comprises an inner core comprising the drug which possesses

(a) a free acid group which can be converted into an alkali metal salt and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

18. (Cancelled).

19. (Amended) A method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and/or inflammatory bowel disease, [which method comprises] the method comprising

administering to a patient in need of treatment a composition [according to any one of Claims 1 to 14 to a patient, preferably a human patient] comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

20. (Cancelled).

21. (New) The composition of claim 1 wherein the pellets are compressed into tablets which are coated to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

22. (New) The composition of claim 1 wherein the core is between about 0.3 to 5 mm in size.

11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000  
1001  
1002  
1003  
1004  
1005  
1006  
1007  
1008  
1009  
1010  
1011  
1012  
1013  
1014  
1015  
1016  
1017  
1018  
1019  
1020  
1021  
1022  
1023  
1024  
1025  
1026  
1027  
1028  
1029  
1030  
1031  
1032  
1033  
1034  
1035  
1036  
1037  
1038  
1039  
1040  
1041  
1042  
1043  
1044  
1045  
1046  
1047  
1048  
1049  
1050  
1051  
1052  
1053  
1054  
1055  
1056  
1057  
1058  
1059  
1060  
1061  
1062  
1063  
1064  
1065  
1066  
1067  
1068  
1069  
1070  
1071  
1072  
1073  
1074  
1075  
1076  
1077  
1078  
1079  
1080  
1081  
1082  
1083  
1084  
1085  
1086  
1087  
1088  
1089  
1090  
1091  
1092  
1093  
1094  
1095  
1096  
1097  
1098  
1099  
1100  
1101  
1102  
1103  
1104  
1105  
1106  
1107  
1108  
1109  
1110  
1111  
1112  
1113  
1114  
1115  
1116  
1117  
1118  
1119  
1120  
1121  
1122  
1123  
1124  
1125  
1126  
1127  
1128  
1129  
1130  
1131  
1132  
1133  
1134  
1135  
1136  
1137  
1138  
1139  
1140  
1141  
1142  
1143  
1144  
1145  
1146  
1147  
1148  
1149  
1150  
1151  
1152  
1153  
1154  
1155  
1156  
1157  
1158  
1159  
1160  
1161  
1162  
1163  
1164  
1165  
1166  
1167  
1168  
1169  
1170  
1171  
1172  
1173  
1174  
1175  
1176  
1177  
1178  
1179  
1180  
1181  
1182  
1183  
1184  
1185  
1186  
1187  
1188  
1189  
1190  
1191  
1192  
1193  
1194  
1195  
1196  
1197  
1198  
1199  
1200  
1201  
1202  
1203  
1204  
1205  
1206  
1207  
1208  
1209  
1210  
1211  
1212  
1213  
1214  
1215  
1216  
1217  
1218  
1219  
1220  
1221  
1222  
1223  
1224  
1225  
1226  
1227  
1228  
1229  
1230  
1231  
1232  
1233  
1234  
1235  
1236  
1237  
1238  
1239  
1240  
1241  
1242  
1243  
1244  
1245  
1246  
1247  
1248  
1249  
1250  
1251  
1252  
1253  
1254  
1255  
1256  
1257  
1258  
1259  
1260  
1261  
1262  
1263  
1264  
1265  
1266  
1267  
1268  
1269  
1270  
1271  
1272  
1273  
1274  
1275  
1276  
1277  
1278  
1279  
1280  
1281  
1282  
1283  
1284  
1285  
1286  
1287  
1288  
1289  
1290  
1291  
1292  
1293  
1294  
1295  
1296  
1297  
1298  
1299  
1300  
1301  
1302  
1303  
1304  
1305  
1306  
1307  
1308  
1309  
1310  
1311  
1312  
1313  
1314  
1315  
1316  
1317  
1318  
1319  
1320  
1321  
1322  
1323  
1324  
1325  
1326  
1327  
1328  
1329  
1330  
1331  
1332  
1333  
1334  
1335  
1336  
1337  
1338  
1339  
1340  
1341  
1342  
1343  
1344  
1345  
1346  
1347  
1348  
1349  
1350  
1351  
1352  
1353  
1354  
1355  
1356  
1357  
1358  
1359  
1360  
1361  
1362  
1363  
1364  
1365  
1366  
1367  
1368  
1369  
1370  
1371  
1372  
1373  
1374  
1375  
1376  
1377  
1378  
1379  
1380  
1381  
1382  
1383  
1384  
1385  
1386  
1387  
1388  
1389  
1390  
1391  
1392  
1393  
1394  
1395  
1396  
1397  
1398  
1399  
1400  
1401  
1402  
1403  
1404  
1405  
1406  
1407  
1408  
1409  
1410  
1411  
1412  
1413  
1414  
1415  
1416  
1417  
1418  
1419  
1420  
1421  
1422  
1423  
1424  
1425  
1426  
1427  
1428  
1429  
1430  
1431  
1432  
1433  
1434  
1435  
1436  
1437  
1438  
1439  
1440  
1441  
1442  
1443  
1444  
1445  
1446  
1447  
1448  
1449  
1450  
1451  
1452  
1453  
1454  
1455  
1456  
1457  
1458  
1459  
1460  
1461  
1462  
1463  
1464  
1465  
1466  
1467  
1468  
1469  
1470  
1471  
1472  
1473  
1474  
1475  
1476  
1477  
1478  
1479  
1480  
1481  
1482  
1483  
1484  
1485  
1486  
1487  
1488  
1489  
1490  
1491  
1492  
1493  
1494  
1495  
1496  
1497  
1498  
1499  
1500  
1501  
1502  
1503  
1504  
1505  
1506  
1507  
1508  
1509  
1510  
1511  
1512  
1513  
1514  
1515  
1516  
1517  
1518  
1519  
1520  
1521  
1522  
1523  
1524  
1525  
1526  
1527  
1528  
1529  
1530  
1531  
1532  
1533  
1534  
1535  
1536  
1537  
1538  
1539  
1540  
1541  
1542  
1543  
1544  
1545  
1546  
1547  
1548  
1549  
1550  
1551  
1552  
1553  
1554  
1555  
1556  
1557  
1558  
1559  
1560  
1561  
1562  
1563  
1564  
1565  
1566  
1567  
1568  
1569  
1570  
1571  
1572  
1573  
1574  
1575  
1576  
1577  
1578  
1579  
1580  
1581  
1582  
1583  
1584  
1585  
1586  
1587  
1588  
1589  
1590  
1591  
1592  
1593  
1594  
1595  
1596  
1597  
1598  
1599  
1600  
1601  
1602  
1603  
1604  
1605  
1606  
1607  
1608  
1609  
1610  
1611  
1612  
1613  
1614  
1615  
1616  
1617  
1618  
1619  
1620  
1621  
1622  
1623  
1624  
1625  
1626  
1627  
1628  
1629  
1630  
1631  
1632  
1633  
1634  
1635  
1636  
1637  
1638  
1639  
1640  
1641  
1642  
1643  
1644  
1645  
1646  
1647  
1648  
1649  
1650  
1651  
1652  
1653  
1654  
1655  
1656  
1657  
1658  
1659  
1660  
1661  
1662  
1663  
1664  
1665  
1666  
1667  
1668  
1669  
1670  
1671  
1672  
1673  
1674  
1675  
1676  
1677  
1678  
1679  
1680  
1681  
1682  
1683  
1684  
1685  
1686  
1687  
1688  
1689  
1690  
1691  
1692  
1693  
1694  
1695  
1696  
1697  
1698  
1699  
1700  
1701  
1702  
1703  
1704  
1705  
1706  
1707  
1708  
1709  
1710  
1711  
1712  
1713  
1714  
1715  
1716  
1717  
1718  
1719  
1720  
1721  
1722  
1723  
1724  
1725  
1726  
1727  
1728  
1729  
1730  
1731  
1732  
1733  
1734  
1735  
1736  
1737  
1738  
1739  
1740  
1741  
1742  
1743  
1744  
1745  
1746  
1747  
1748  
1749  
1750  
1751  
1752  
1753  
1754  
1755  
1756  
1757  
1758  
1759  
1760  
1761  
1762  
1763  
1764  
1765  
1766  
1767  
1768  
1769  
1770  
1771  
1772  
1773  
1774  
1775  
1776  
1777  
1778  
1779  
1780  
1781  
1782  
1783  
1784  
1785  
1786  
1787  
1788  
1789  
1790  
1791  
1792  
1793  
1794  
1795  
1796  
1797  
1798  
1799  
1800  
1801  
1802  
1803  
1804  
1805  
1806  
1807  
1808  
1809  
1810  
1811  
1812  
1813  
1814  
1815  
1816  
1817  
1818  
1819  
1820  
1821  
1822  
1823  
1824  
1825  
1826  
1827  
1828  
1829  
1830  
1831  
1832  
1833  
1834  
1835  
1836  
1837  
1838  
1839  
1840  
1841  
1842  
1843  
1844  
1845  
1846  
1847  
1848  
1849  
1850  
1851  
1852  
1853  
1854  
1855  
1856  
1857  
1858  
1859  
1860  
1861  
1862  
1863  
1864  
1865  
1866  
1867  
1868  
1869  
1870  
1871  
1872  
1873  
1874  
1875  
1876  
1877  
1878  
1879  
1880  
1881  
1882  
1883  
1884  
1885  
1886  
1887  
1888  
1889  
1890  
1891  
1892  
1893  
1894  
1895  
1896  
1897  
1898  
1899  
1900  
1901  
1902  
1903  
1904  
1905  
1906  
1907  
1908  
1909  
1910  
1911  
1912  
1913  
1914  
1915  
1916  
1917  
1918  
1919  
1920  
1921  
1922  
1923  
1924  
1925  
1926  
1927  
1928  
1929  
1930  
1931  
1932  
1933  
1934  
1935  
1936  
1937  
1938  
1939  
1940  
1941  
1942  
1943  
1944  
1945  
1946  
1947  
1948  
1949  
1950  
1951  
1952  
1953  
1954  
1955  
1956  
1957  
1958  
1959  
1960  
1961  
1962  
1963  
1964  
1965  
1966  
1967  
1968  
1969  
1970  
1971  
1972  
1973  
1974  
1975  
1976  
1977  
1978  
1979  
1980  
1981  
1982  
1983  
1984  
1985  
1986  
1987  
1988  
1989  
1990  
1991  
1992  
1993  
1994  
1995  
1996  
1997  
1998  
1999  
2000  
2001  
2002  
2003  
2004  
2005  
2006  
2007  
2008  
2009  
2010  
2011  
2012  
2013  
2014  
2015  
2016  
2017  
2018  
2019  
2020  
2021  
2022  
2023  
2024  
2025  
2026  
2027  
2028  
2029  
2030  
2031  
2032  
2033  
2034  
2035  
2036  
2037  
2038  
2039  
2040  
2041  
2042  
2043  
2044  
2045  
2046  
2047  
2048  
2049  
2050  
2051  
2052  
2053  
2054  
2055  
2056  
2057  
2058  
2059  
2060  
2061  
2062  
2063  
2064  
2065  
2066  
2067  
2068  
2069  
2070  
2071  
2072  
2073  
2074  
2075  
2076  
2077  
2078  
2079  
2080  
2081  
2082  
2083  
2084  
2085  
2086  
2087  
2088  
2089  
2090  
2091  
2092  
2093  
2094  
2095  
2096  
2097  
2098  
2099  
2100  
2101  
2102  
2103  
2104  
2105  
2106  
2107  
2108  
2109  
2110  
2111  
2112  
2113  
2114  
2115  
2116  
2117  
2118  
2119  
2120  
2121  
2122  
2123  
2124  
2125  
2126  
2127  
2128  
2129  
2130  
2131  
2132  
2133  
2134  
2135  
2136  
2137  
2138  
2139  
2140  
2141  
2142  
2143  
2144  
2145  
2146  
2147  
2148  
2149  
2150  
2151  
2152  
2153  
2154  
2155  
2156  
2157  
2158  
2159  
2160  
2161  
2162  
2163  
2164  
2165  
2166  
2167  
2168  
2169  
2170  
2171  
2172  
2173  
2174  
2175  
2176  
2177  
2178  
2179  
2180  
2181  
2182  
2183  
2184  
2185  
2186  
2187  
2188  
2189  
2190  
2191  
2192  
2193  
2194  
2195  
2196  
2197  
2198  
2199  
2200  
2201  
2202  
2203  
2204  
2205  
2206  
2207  
2208  
2209  
2210  
2211  
2212  
2213  
2214  
2

PCT/PTO 02 APR 1999

COLONIC DELIVERY OF WEAK ACID DRUGS

This invention relates to novel controlled-release formulations of drugs with pKa values of between 2.0 and 9.0.

5

Drugs that have weak basic functions and/or weak acid functions (i.e. those with pKa values of between 2.0 and 9.0) often have a low and/or variable solubility at pH values normally experienced in the colon (i.e. between 4.5 and 8.0). Consequently, if a drug is delivered to the colon for e.g. local  
10 action, the dissolution of the drug from the tablet, pellet or capsule formulation can be extremely variable, resulting in unsatisfactory controlled release profiles.

Ridogrel ((E)-5-[[[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]amino]-oxy]pentanoic acid; Janssen Pharmaceutica, Belgium; see US patent  
15 4,963,573) is an example of a drug in which such problems have been found to occur. Ridogrel is a development compound which has been indicated for use in the treatment of *inter alia* inflammatory bowel diseases including Crohn's disease and ulcerative colitis. The drug may be  
20 administered orally in simple pharmaceutical formulations. However, it is anticipated that, if the drug could be delivered to the colonic region of the gastrointestinal tract in a slow release (rate-controlled) fashion, advantages would result. For example, delivery to the colon is likely to concentrate the drug at the required site of action and therefore prevent unwanted  
25 absorption of the drug into the systemic circulation from the small intestine. Further, the controlled release nature of such a formulation is likely to provide good distribution of the drug to the various regions of the large intestine.

General methods for the site specific delivery of drugs to the large bowel have been described in the prior art, including the applicant's pending international patent application WO 95/35100, which discloses the coating of starch capsules with polymers that degrade or dissolve under the conditions found within the different regions of the gastrointestinal tract. In this prior art document, a preferred system was disclosed as comprising a starch capsule coated with a mixture of methacrylate polymers. These polymers only dissolve at pH values above 4.5, thereby allowing a formulation to remain intact in the stomach. Upon entry into the small intestine, the coating on the capsule begins to dissolve. By adjustment of the thickness of the coating of such formulations, it is possible for the capsule to reach the terminal ileum or ascending colon before releasing its contents.

Another granted patent (EP 513 035) describes how a similar effect can be achieved using polymers that are degraded specifically in the colonic environment due to the unique reducing conditions therein. Polymers based upon disulphide bonds have been shown to be effective both *in vitro* and *in vivo*.

20

Alternatively, compositions can be delivered to the colon using other known colon targeting systems. Some examples, which are not exhaustive, are as follows:

25 The Time Clock Release System™ (Pozzi *et al*, APV Course on Pulsatile Drug Delivery, Konigswinter, 20 May 1992) is a tablet system where a tablet core containing the active drug is coated with a layer of pharmaceutical excipients. The excipients hydrate causing the surface layer to burst at a set time. The Pulsincap™ system is an oral pulsatile delivery

system which may be configured to release its drug content at a predetermined time or place within the gastrointestinal tract. The device essentially consists of an impermeable capsule body which contains the drug, sealed at the neck orifice with a hydrogel plug. A normal gelatin cap  
5 is then placed onto the body of the device. After ingestion, the gelatin cap dissolves allowing the plug to hydrate. At a predetermined and controlled time, the swollen plug is ejected from the body of the device, thereby releasing the capsule contents and enabling the drug to be released (Wilding et al., Pharm. Res. 9, 654, 1992 and Binns et al., 3rd Eur. Symp. Control.  
10 Drug Del., Abstract Book, 1994, p124).

Another system which may be used is the time controlled explosion system, as described in US 4,871,549.

15 The problem to be solved in the case of the drug ridogrel and similar molecules (for example those which are weakly ionisable in nature, in particular those which are useful in the treatment of inflammation of the intestines and especially thromboxane synthase  $A_2$  inhibitors and thromboxane  $A_2$ /prostaglandin endoperoxide receptor antagonists such as  
20 those disclosed in US 4,963,573) is one of (a) achieving a controlled release formulation that will provide good distribution throughout the colon in order to optimise treatment of affected sites, and (b) for such release to be constant (i.e. as near to zero order as possible) and predictable (i.e. reproducible) over an extended period of time.

25

Controlled release formulations of drugs which target the colon in particular may also be useful for the systemic delivery of therapeutic agents as "once daily" products.

A variety of formulation principles have been disclosed in the prior art for the controlled release of drugs that are weak acids or weak bases.

However, it has been found that, in order for a formulation to be distributed evenly at the target site, a multiparticulate pellet formulation is preferred.

5 Pellets may be formed by a number of different processes, all well known in the art, including extrusion and spheronisation, as well as the coating of the drug material onto preformed sugar spheres (also known as non-pariels).

The drug can be coated onto non-pariels using techniques which are familiar to those skilled in the art. A controlled release layer may then be coated on  
10 top of the drug layer so as to provide a diffusional barrier. Unfortunately, with drugs such as ridogrel, we have found that a simple diffusional barrier does not provide a satisfactory product. This is because ridogrel has weakly basic functions and a carboxylic acid function and the solubility of the drug in the colonic pH range (4.5 to 8.0) is therefore low, resulting in extremely  
15 variable dissolution of the drug at such pH values. Thus, a simple formulation, wherein ridogrel is coated onto non-pariel beads, and then overcoated with a rate-controlling membrane, does not result in a formulation possessing a satisfactory release profile.

20 However, we have found, surprisingly, that it is possible to achieve a satisfactory formulation comprising drugs such as ridogrel by choosing, instead of the drug itself, an appropriate salt (e.g. alkali metal salt) that has pH independent solubility characteristics. The salt of the drug should be at least 10 times more soluble than the free acid form of the drug and, more  
25 preferably, greater than 100 times more soluble, as measured in deionized water at the relevant pH range (i.e. 4.5 to 8.0) at 37°C. By "more soluble" we mean that the salt is more soluble over the entire pH range of 4.5 to 8.0. It is then found, surprisingly, that the coated pellet system gives an almost pH independent release profile under *in vitro* conditions as tested in the USP

type 2 dissolution apparatus (The United States Pharmacopoeia, USP23, 1994, page 1791-1793), for example as described hereinafter.

The pellet system comprising drug may be coated with a coating material (a  
5 rate controlling membrane). The nature and thickness of this coating material may be altered (for example as described hereinafter) to provide a controlled release formulation which will, for example, release the drug over a period of up to 5 hours or over a longer period of up to 12 hours. The present invention thus provides a controlled release formulation  
10 comprising an inner core containing, or coated with, a drug and subsequently coated with a rate-controlling membrane that determines drug release, of a drug that contains a weak acid function with a pKa in the range 2.0 to 9.0 (e.g. 3.0 to 9.0) that can be converted into an alkali metal salt wherein the drug is present as a salt that displays higher solubility at pH 4.5  
15 to 8.0 (e.g. 5.0 to 7.0) than the corresponding compound containing a free acid group.

Thus, according to a first aspect of the invention, there is provided a controlled release formulation including an inner core comprising, or coated  
20 with, a drug, which drug possesses (a) a free acid group which can be converted into an alkali metal salt and (b) a pKa in the range 2.0 to 9.0 (e.g. 3.0 to 9.0), which inner core is subsequently coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 (e.g. 5.0 to 7.0) than the  
25 corresponding compound containing a free acid group (referred to hereinafter as "the compositions according to the invention").

Drugs which may be employed in the compositions according to the invention include those which have a rapidly changing solubility in the pH

range 4.5 to 8.0 (i.e. the pH range found in the colon under normal conditions and/or those conditions reported to exist in acute conditions such as ulcerative colitis). Drugs which may be employed include ridogrel, other thromboxane synthase  $A_2$  inhibitors and thromboxane  $A_2$ /prostaglandin endoperoxide receptor antagonists (such as those disclosed in US 4,963,573), and sodium cromoglycate. Particularly preferred drugs include ridogrel.

Suitable salts of the weak acid drugs include ammonium salts and particularly alkali metal salts such as, but not limited to, sodium and potassium salts. Such salts may be prepared in accordance with techniques which are well known to those skilled in the art, including, in the case of alkali metal salts, dissolving the drug in a solution of the relevant hydroxide. For example, an excess of drug may be suspended in the hydroxide solution and stirred for 24 hours. The suspended material may then be removed by filtration and centrifugation and the salt recovered from the filtrate by removal of the water (e.g. using a vacuum oven or by lyophilisation).

The salts may also be prepared as part of a preparation process for the coating of the inner cores. In this case, drug is dissolved in, for example, an appropriate hydroxide solution at a suitable concentration (e.g. 1M) and the pH is adjusted to about 8 by adding acid, such as 0.1M HCl. The salt solution may then be added to a solution of a binder (such as povidone) and the pH adjusted to about 8 (again). This mixture may then be coated onto the inner cores using, for example, a spray coating apparatus. The pellets may, if necessary, be overcoated with a thin layer of plasticised HPMC, which may act as a "primer", in order to obtain a better coating. The inner cores may then be overcoated with the controlled release coating layer (rate-

controlling membrane), which may, for example, consist of Eudragit® RS30D, triethyl citrate and talc, and subsequently dried. The pellets may then be filled into capsules to be coated for delivery to the colon, or compressed into tablets which are then coated.

5

The inner core may comprise drug salt. Drug salt may be incorporated into the inner core during the manufacture of the latter, for example by extrusion/spheronisation.

10 Inner cores which may be employed in the compositions according to the invention include sugar spheres (non-pariels). Suitable sizes of inner cores which may be employed in the compositions according to the invention are in the range 0.3 to 5 mm.

15 In general, the preferred controlled release coating materials which may be employed in the rate-controlling membrane of the compositions according to the invention include those which form a water-insoluble but water-permeable layer and from which release of drug is by diffusion through the layer. By "water-insoluble" we mean "sparingly soluble" as defined in the  
20 British Pharmacopoeia (1988). By "water-permeable" we mean that at least 10% of water, held continuously in contact with the layer, will penetrate the layer within two hours (the degree of permeation may be measured in accordance with techniques which are well known to those skilled in the art). The coating polymer may be inherently water-permeable or become  
25 water-permeable through the incorporation of other additives such as plasticisers or pore forming agents. Suitable coating polymers include methacrylate copolymers, ethylcellulose, etc. Preferred coating materials are the permeable, water insoluble grades of pharmaceutical polymethacrylates (Eudragit® RL100, Eudragit RS100/RS30D, Eudragit

NE30D, Rohm Pharma, Darmstadt, Germany) and ethylcellulose. Eudragit RL100 and RS100 contain quaternary ammonium groups which may interact with ionised weakly acidic drugs and hence the most preferred coating materials are ethylcellulose and Eudragit NE30D. Ethylcellulose may be applied as a solution in an organic solvent or as a proprietary water-based latex preparation (e.g. Aquacoat®, FMC, Philadelphia, USA or Surelease®, Colorcon, West Point, USA).

The thickness of the rate-controlling membrane required for use in the compositions according to the invention will depend on the permeability of the polymer to the drug in question and the duration of release required from the coated formulation. However, the amount employed will typically be in the range 2% w/w to 25% w/w of the formulation, or will be an amount to produce a thickness in the range 80 µm to 300 µm.

The compositions according to the invention may be adapted to deliver therapeutic agent to the colonic region of the gastrointestinal tract, especially the proximal colon. Preferably, a means is provided to prevent release of drug until the formulation reaches the colonic region.

By "colonic region of the gastrointestinal tract" we mean the terminal ileum and the colon.

The compositions according to the invention, may thus be filled into the various known delivery systems intended for targeting the colonic region, including those described above, and including the coated capsules described above. Alternatively, the compositions according to the invention may be further coated with an enteric layer that slowly dissolves within the small intestine to allow exposure of the rate-controlling membrane to the

liquid in the terminal ileum and/or the colon for subsequent release. In a similar fashion to the coated starch capsules disclosed in international patent application WO 95/35100, the coating may be an enteric polymer that dissolves in the small intestine or a polymeric or polysaccharide material that is not degraded until it meets the specific conditions found in the colon. Such degradation may be through direct chemical effect, e.g. the degradation of disulphide bonds under reducing conditions, or the degradation of polysaccharide materials under the effects of the microflora found within the colon.

Preferred coating materials for targeting to the colon, which may be used in capsules, tablets or pellets including the compositions according to the invention, are those which dissolve at pH of 4.5 or above. In this way, the coatings only begin to dissolve once they have left the stomach and have entered the small intestine. A thick layer of coating is thus preferably provided which will dissolve in about 2 to 5 hours, thereby allowing the capsule underneath to break-up only when it has reached the terminal ileum and/or the colon. Such a coating can be made from a variety of polymers such as cellulose acetate trimellitate (CAT), hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP) and shellac, as described by Healy in his article "Enteric Coatings and Delayed Release", Chapter 7 in *Drug Delivery to the Gastrointestinal Tract*, eds. Hardy *et al*, Ellis Horwood, Chichester, 1989. For coatings of the polymers, a thickness of 150 to 300  $\mu\text{m}$  is suitable.

Especially preferred materials are methylmethacrylates or copolymers of methacrylic acid and methylmethacrylate. Such materials are available as Eudragit® enteric polymers (Rohm Pharma, Darmstadt, Germany; see above). These are copolymers of methacrylic acid and methylmethacrylate.

Preferred compositions are based on Eudragit L100 and Eudragit S100. Eudragit L100 dissolves at pH 6 and upwards and comprises 48.3% methacrylic acid units per g of dry substance; Eudragit S100 dissolves at pH 7 and upwards and comprises 29.2% methacrylic acid units per g of dry substance. Preferred coating compositions are based on Eudragit L100 and Eudragit S100 in the range 100 parts L100:0 parts S100 to 20 parts L100:80 parts S100. The most preferable range is 70 parts L100:30 parts S100 to 80 parts L100:20 parts S100. As the pH at which the coating begins to dissolve increases, the thickness necessary to achieve colon specific delivery decreases. For formulations where the ratio of Eudragit L100:S100 is high, a coat thickness of the order 150-200  $\mu\text{m}$  is preferable. This is equivalent to 70-110 mg of coating for a size 0 capsule. For coatings where the ratio Eudragit L100:S100 is low, a coat thickness of the order 80 to 120  $\mu\text{m}$  is preferable, which is equivalent to 30 to 60 mg coating for a size 0 capsule.

The colonic region has a large population of microbial anaerobic organisms providing reducing conditions. Thus, the coating may suitably comprise a material which is redox-sensitive. Such coatings may comprise azopolymers which may, for example, consist of a random copolymer of styrene and hydroxyethyl methacrylate, cross-linked with divinylazobenzene synthesised by free radical polymerisation (the azopolymer being broken down enzymatically and specifically in the colon), or disulphide polymers (see PCT/BE91/00006 and Van den Mooter, *Int. J. Pharm.* **87**, 37 (1992)).

Other materials which may be used to provide release in the colon include amylose. For example, a coating composition can be prepared by mixing amylose-butan-1-ol complex (glassy amylose) with Ethocel® aqueous dispersion (Milojevic *et al.*, *J. Control. Rel.*, **38**, 75 (1996)), or a coating formulation comprising an inner coating of glassy amylose and an outer

coating of cellulose or acrylic polymer material (Allwood *et al.*, GB9025373.3), calcium pectinate (Rubenstein *et al.*, Pharm. Res., **10**, 258, (1993)), pectin, a polysaccharide which is totally degraded by colonic bacterial enzymes (Ashford *et al.*, Br. Pharm. Conference, 1992 Abstract 5 13), chondroitin sulphate (Rubenstein *et al.*, Pharm. Res. **9**, 276, 1992) and resistant starches (Allwood *et al.*, PCT WO89/11269, 1989), dextran hydrogels (Hovgaard and Brøndsted, 3rd Eur. Symp. Control. Drug Del., Abstract Book, 1994, 87), modified guar gum, such as borax modified guar gum (Rubenstein and Gliko-Kabir, S.T.P. Pharma Sciences **5**, 41 (1995)), 10 *p*-cyclodextrin (Sie ke *et al.*, Eur. J. Pharm. Biopharm. **40** (suppl.), 335 (1994)), saccharide containing polymers, by which we include a polymeric construct comprising a synthetic oligosaccharide-containing biopolymer, including methacrylic polymers covalently coupled to oligosaccharides such as cellobiose, lactulose, raffinose, and stachyose, or saccharide-containing 15 natural polymers including modified mucopolysaccharides such as cross-linked chondroitin sulfate and metal pectin salts, for example calcium pectate (Sintov and Rubenstein; PCT/US91/03014); methacrylate-galactomannan (Lehmann and Dreher, Proc. Int. Symp. Control. Rel. Bioact. Mater. **18**, 331 (1991)), pH-sensitive hydrogels (Kopecek *et al.*, J. Control. Rel. **19**, 121 (1992)) and resistant starches, e.g. glassy amylose, 20 that are not broken down by the enzymes in the upper gastrointestinal tract but are degraded by enzymes in the colon.

It will be well understood by those skilled in the art that further excipients 25 may be employed in the compositions according to the invention. For example, further excipients which may be employed include diluents such as microcrystalline cellulose (e.g. Avicel®, FMC), lactose, dicalcium phosphate and starch(es); disintegrants such as microcrystalline cellulose, starch(es) and cross-linked carboxymethylcellulose; lubricants such as

magnesium stearate and stearic acid; granulating agents such as povidone; and release modifiers such as hydroxypropyl methylcellulose and hydroxypropyl cellulose. Suitable quantities of such excipients will depend upon the identity of the active ingredient(s) and particular dosing form which is used.

Appropriate quantities of drug salts which may be employed in the compositions according to the invention will depend upon the agent which is used. However, it will be clear to the skilled person that doses of drug salts can be readily determined non-inventively. Suitable doses for selected drugs in the present invention (e.g. ridogrel) are in the range 1 to 200 mg, preferably 2 to 100 mg and more preferable, 5 to 50 mg.

Compositions according to the invention have been found to have the advantage that they provide an improved release profile in respect of drugs which have a rapidly changing solubility, and therefore an extremely variable dissolution, in the colonic pH range (4.5 to 8.0).

Thus, according to a further aspect of the invention there is provided a method of improving the release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0 which method comprises administering a composition according to the invention to a patient, preferably a human patient.

In view of the advantageous properties of the compositions according to the invention, they are useful in the treatment of conditions such as ulcerative colitis, Crohn's disease, irritable bowel syndrome and/or inflammatory bowel disease, when adapted for delivery to the colonic region.

According to a further aspect of the invention there is provided a method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome and/or inflammatory bowel disease which method comprises administering a composition according to the invention to the colonic region of a patient,  
5 preferably a human patient.

### Brief Description of the Figures

Figure 1 shows the release of ridogrel at pH 6 and pH 7 from 0.61 to 0.7  
10 mm pellets coated with 3.7% Eudagrit RS (USP method 2; 37°C).

Figure 2 shows the dissolution of (a) ridogrel and (b) sodium ridogrel at pH 5, 6 and 7.

15 Figure 3 shows the release of ridogrel (as the sodium salt) at pH 5, 6 and 7 from 0.6 to 0.71 mm pellets coated with 19% w/w Eudagrit RS (USP method 2; 37°C).

Figure 4 shows the release of ridogrel (as the sodium salt) from 1 to 1.18  
20 mm pellets with three levels of Aquacoat coating (USP method 2; 37°C).

Figure 5 shows the release of ridogrel (as the sodium salt) at pH 5, 6 and 7 from 1 to 1.18 mm pellets containing 14% Aquacoat coating (USP method 2; 37°C).

25

Figure 6 shows the dissolution performance of starch capsules containing inner cores comprising sodium ridogrel.

Figure 7 shows the plasma profiles of three colon targeted formulations as determined in a human clinical trial, pharmacoscintigraphy study.

The invention is illustrated, but in no way limited, by the following examples.

#### Example 1 (Comparative example)

##### Preparing ridogrel pellets coated with polymethacrylate (Eudragit RS)

A solution of 20 g of ridogrel (Janssen Pharmaceutica; Belgium) and 2 g of povidone (Kollidon 30) in 250 mL of ethanol was prepared. This solution was spray-coated onto 400 g of sugar spheres (600-710  $\mu$ m, NP Pharma, France) using an Aeromatic STREA-1 coater. The pellets were assayed for ridogrel content by a spectrophotometric method. To prepare the coating solution of sustained release polymer, 35 g of talc was first dispersed in 250 mL of water and 9 g of triethyl citrate was added. 150 mL of Eudragit RS30D (Rohm Pharma) was then added to the talc dispersion. 280 g of the ridogrel-coated pellets were then coated with the Eudragit solution in the STREA-1 using an inlet temperature of 50°C. 100 mL of solution was applied to the pellets. The pellets were then dried overnight at 40°C and assayed for ridogrel content using a spectrophotometric method (UV).

The dissolution performance of the pellets was measured using the BP/USP method 2 (USP23, 1994, page 1791-1793; paddles, 50 rpm) with 900 mL of either pH 6 or pH 7 phosphate buffer as the test medium. In Figure 1, the dissolution performance of the pellets is shown. Compared to the performance of the pellets at pH 7, there was a substantial reduction in the rate of drug release at pH 6. For example, after 4 hours, approximately 24% of the ridogrel had been released at pH 6, compared to 74% at pH 7.

### Example 2

#### Solubility of ridogrel and sodium ridogrel

In accordance with the invention, sodium ridogrel was prepared as follows:

- i) 0.1 g of sodium hydroxide was dissolved in 20 mL of water;
  - 5        ii) 1.5 g of ridogrel was added to the sodium hydroxide solution to form a suspension;
  - iii) the ridogrel suspension was placed into a sonic bath for 10 minutes;
  - iv) the suspension was passed through a 0.45  $\mu$ m membrane filter,
  - 10        the filtrate was collected, diluted by adding 20 mL of water, and lyophilised overnight; and
  - v) the lyophilised sodium ridogrel was gently milled in a mortar to produce a fine powder.
- 15        Into each of three size 2 hard gelatin capsules was weighed 10 mg of ridogrel. Into another three capsules was weighed 10 mg of the sodium ridogrel lyophilisate. The dissolution of ridogrel and sodium ridogrel into 900 mL of phosphate buffer at pH 5, 6 and 7 was tested (USP apparatus 2, 100 rpm). The dissolution rate of ridogrel (as the parent acid) increased as
- 20        the pH was raised (Figure 2a). In contrast, the rate of dissolution of sodium ridogrel was largely independent of pH (Figure 2b).

Therefore there was a significant reduction in the rate of dissolution of ridogrel as the pH was reduced from 7 to 5, the pH range likely to be

25        encountered in the large intestine. However, in this pH range, the sodium salt of ridogrel had a greatly improved dissolution rate.

### Example 3

#### Preparation of pellets coated with sodium ridogrel and Eudragit

Pellets were prepared containing the sodium salt of ridogrel. 20 g of ridogrel was dissolved in approximately 60 mL of 1M sodium hydroxide solution. The solution of sodium ridogrel was adjusted down to pH 8 by adding 0.1M hydrochloric acid and made up to 100 mL with water. 40 g of povidone (Kollidon 30; BASF) was dissolved in 200 mL of water. The povidone solution was added to the ridogrel solution and a precipitate was formed, which was dissolved by adding sodium hydroxide to adjust the solution to pH 8. The povidone/sodium ridogrel solution was applied to 1 kg of sugar spheres (0.6-0.71 mm) using the Aeromatic STREA-1 coater. After coating, the pellets were relatively tacky which could have been due to the hygroscopic nature of the povidone and/or the sodium ridogrel. To remove this tackiness, the pellets were overcoated with a thin layer of HPMC: The HPMC solution was prepared by dissolving 30 g of Methocel® E5 in 600 mL of water and adding 3 g of PEG400 as a plasticiser. The pellets were assayed for ridogrel content.

450 mL of Eudragit coating solution was prepared as follows: 150 mL of Eudragit RS30D, 9 g of triethyl citrate, 35 g of talc, 250 mL of water. The solution was applied to 400 g of sodium ridogrel/povidone/HPMC pellets. The coated pellets were dried overnight at 40°C. The pellets were assayed for ridogrel content.

The dissolution performance of the pellets at pH 5, 6 and 7 is shown in Figure 3. There was a small reduction in the rate of drug release as the pH was decreased. This demonstrated that the rate of release of ridogrel as the sodium salt was largely independent of pH, which was in marked contrast to pellets containing ridogrel as the parent acid (see Figure 1).

#### Example 4

##### Preparation of pellets coated with sodium ridogrel and ethylcellulose

Pellets were prepared with an ethylcellulose outer layer. A water-based  
5 ethylcellulose preparation, Aquacoat® (FMC, Philadelphia), was used in  
order to eliminate the use of organic solvents in the coating process. Pellets  
were prepared as follows:

20 g of ridogrel was weighed into a beaker and dissolved in 56 mL of 1M  
10 sodium hydroxide solution. 40 g of povidone (Kollidon K30) was weighed  
into a large beaker and dissolved in 500 mL of water. The ridogrel solution  
was added to the povidone solution. The pH change resulted in precipitation  
of ridogrel. Sodium hydroxide solution was added to dissolve the ridogrel.  
The pH of the solution was adjusted to pH 8 using 0.1M hydrochloric acid  
15 and made up to 600 mL with water. 1 kg of sugar spheres (1.00-1.18 mm  
diameter) were coated with the sodium ridogrel/povidone solution using the  
Aeromatic STREA-1 coater (inlet temperature was 55°C).

An overcoat of HPMC was applied to the sodium ridogrel/povidone layer.  
20 The HPMC solution was prepared by dispersing 20 g of HPMC  
(Methocel® E5) in 200 mL of hot water. The dispersion was cooled in ice  
(whilst being stirred) and 2 g of PEG400 was added as a plasticiser. The  
solution was made up to 400 mL with water. The HPMC solution was  
applied using the STREA-1 at an inlet temperature of 55°C. The completed  
25 pellets were left to dry overnight at room temperature. The Aquacoat  
mixture was prepared by stirring together 300 mL of Aquacoat and 21.6 g  
of dibutyl sebacate for 1 hour, followed by the addition of 300 mL of water.  
500 g of sodium ridogrel/povidone/HPMC pellets were transferred to the  
Aeromatic and coated with the Aquacoat mixture (coating temperature

40°C). Pellet samples (20 g) were collected at intermediate points in the coating run, after the application of approximately 300 mL and 450 mL of the coating solution. After coating, the pellet samples were spread into trays and dried overnight at 60°C.

5

The dissolution performance of the pellets at pH 7 is shown in Figure 4. The dissolution performance of the pellets containing 14% coating at pH 5, 6 and 7 is shown in Figure 5. Drug release was independent of pH. The release of drug from these samples was complete. This was in contrast to  
10 the Eudragit-coated pellets where drug release was incomplete. This was probably due to an interaction between negatively-charged ridogrel ions and positively charged quaternary ammonium groups within Eudragit RS. Hence ethylcellulose is a preferred polymer for use in preparing ridogrel controlled release pellets.

15

### Example 5

#### Preparation of Formulations for Testing in Human Clinical Trial, Phase 1.

Pellets were prepared with an ethylcellulose outer layer as the rate  
20 controlling membrane. A water based ethylcellulose preparation, Aquacoat® (FMC, Philadelphia) was used. 10 g of ridogrel was weighed into a beaker and dissolved in 28 mL of 1 M sodium hydroxide solution and made up to 100 mL with water. 20 g of povidone (Kollidon K 30) was weighed into a large beaker and dissolved in 200 mL of water. The  
25 ridogrel solution was added to the povidone solution. 1M sodium hydroxide solution was added to dissolve the precipitated ridogrel and the pH was adjusted to 8 with 0.1 M hydrochloric acid.

500 g of sugar pellets (1-1.18 mm in diameter) were coated with the sodium ridogrel/povidone solution using the aromatic STREA-1 coater (inlet temperature 55°C). An overcoat of HPMC was applied to the sodium ridogrel/povidone layer. The HPMC solution was prepared by dispersing 20 g of HPMC (Methocel E5) in 200 mL hot water. The dispersion was cooled in ice (whilst being stirred) and 1 g of PEG 400 was added as a plasticiser and the volume made up to 400 mL with water. The HPMC solution was applied using the STREA - 1 at an inlet temperature of 55°C. The completed pellets were left to dry overnight at room temperature. 30 g of pellets were removed ("immediate release pellets"; A).

The Aquacoat mixture was prepared by stirring together 300 mL of Aquacoat and 21.6 g of dibutyl sebacate for 1 hour, followed by the addition of 300 mL of water. About 500 g of sodium ridogrel/povidone/HPMC pellets were transferred to the Aeromatic STREA-1 coater and coated with Aquacoat mixture (coating temperature 45°C). Pellet samples of 35 g were collected after the application of 450 mL ("8 hour release pellets"; B) and after the application of 600 mL ("12 hour release pellets"; C) of Aquacoat. After coating the pellet samples were spread into trays and dried overnight at 60°C.

The three different pellet samples were filed into starch capsules (Capill) with approximately 425 mg in each capsule. The capsules were coated with a Eudragit solution consisting of Eudragit S100/Eudragit L100 1:3, dibutyl sebacate, talc, isopropanol and water in the Aeromatic STREA - 1 coater. The coating conditions used were drying temperature 25°C, fan speed 6, atomisation pressure 1 bar and application rate 1.5 - 4.0 mL/minute. The weight gain per capsule was 78 mg.

The dissolution performance of the capsules at 37°C for 2 hours in 0.1 M HCl, followed by phosphate buffer, pH 6.8 in a Vankel 6010 dissolution apparatus (baskets rotated at 50 rpm) is shown in Figure 6. (Values are the mean of the two determinations.) The difference in rate of dissolution between the 3 different pellet samples is clearly seen.

### Example 6

#### Phase 1 human clinical trial, pharmacoscintigraphy study

The clinical trial was a four way crossover study in 8 healthy male volunteers, aged 18-35 years. Three of the doses administered were the colon targeted capsule formulations described in Example 5. These formulations were radiolabelled with a gamma emitting isotope (indium - 111). The fourth formulation was a conventional immediate release tablet, and was not radiolabelled. On each study day, blood samples were collected for ridogrel analysis. Plasma samples were analysed by Janssen Pharmaceutica. Of the capsules dosed, 21 disintegrated at the ileocaecal junction or in the colon and two in the lower small intestine. The plasma ridogrel analysis showed that for all three colon targeted formulations, peak plasma concentrations occurred much later than with the conventional tablet (7.5 h, 12.5 - 13 h as compared with 0.9 h). The maximum plasma ridogrel concentrations were much lower for the colon targeted formulations than of the conventional tablet, and plasma concentrations were sustained for a longer period. Furthermore the maximum plasma concentration for the immediate release, colon targeted formulation was higher than for the sustained release formulations. The plasma profiles for the colon targeted formulations are shown in Figure 7. (Values are the mean for all volunteers, omitting those where the dose was

retained in the stomach. For Formulation A,  $n = 6$ ; Formulation B,  $n = 7$ ; Formulation C,  $n = 8$ .)

Claims

1. A controlled release composition including pellets, each comprising an inner core, which core comprises, or is coated with, a drug, which drug  
5 possesses (a) a free acid group which can be converted into an alkali metal salt and (b) a pKa in the range 2.0 to 9.0, which inner core is subsequently coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5. to 8.0 than the corresponding compound containing a free acid group,  
10 and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon.
2. A composition as claimed in Claim 1 wherein the drug is a thromboxane synthase A<sub>2</sub> inhibitor or a thromboxane A<sub>2</sub>/prostaglandin endoperoxide  
15 receptor antagonist.
3. A composition as claimed in Claim 2 wherein the drug is ridogrel.
4. A composition as claimed in any one of Claims 1 to 3, wherein the rate-  
20 controlling membrane comprises a material which forms a water-insoluble but water-permeable layer and from which release of drug is by diffusion through the layer.
5. A composition as claimed in Claim 4, wherein the rate-controlling  
25 membrane is formulated from a methacrylate copolymer or ethylcellulose.
6. A composition as claimed in Claim 5, wherein the rate-controlling membrane is formulated from ethylcellulose or Eudragit NE30D.

7. A composition as claimed in Claim 6 where the rate-controlling membrane is ethylcellulose.
8. A composition as claimed in any one of the preceding claims, wherein  
5 the inner core is a sugar sphere.
9. A composition as claimed in any one of the preceding claims, wherein the salt is at least 10 times more soluble than the free acid form of the drug at pH 4.5 to 8.0 at 37°C.
- 10
10. A composition as claimed in any Claim 9, wherein the salt is at least 100 times more soluble than the free acid form of the drug.
11. A composition as claimed in any one of the preceding claims, wherein  
15 the salt is an alkali metal salt.
12. A composition as claimed in Claim 11, wherein the alkali metal is sodium or potassium.
- 20
13. A composition as claimed in any one of the preceding claims wherein the pellets are administered in a starch capsule coated with a combination of polymethacrylates that is designed to disintegrate and release the pellets in the terminal ileum or in the colon.
- 25
14. A composition as claimed in any one of the preceding claims wherein the drug is used for the treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, inflammatory bowel disease.

15. A process for the preparation of a composition according to any one of the preceding claims which comprises making a salt of the drug and coating said salt onto the inner cores.

5 16. A process as claimed in Claim 15, wherein the salt is prepared as part of a preparation process for the coating of the inner cores.

17. A method of improving the release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0, which comprises  
10 administering a composition according any one of Claims 1 to 14 to a patient, preferably a human patient.

18. The use of a composition according any one of Claims 1 to 14 in the manufacture of a medicament for use in the improved release profile of a  
15 drug with a rapidly changing solubility in the pH range 4.5 to 8.0.

19. A method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome and/or inflammatory bowel disease which method comprises administering a composition according to any one of Claims 1 to  
20 14 to a patient, preferably a human patient.

20. The use of a composition according any one of Claims 1 to 14 in the manufacture of a medicament for the treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome and/or inflammatory bowel  
25 disease.

AMENDED SPECIFICATION  
1984/80

Figure 1

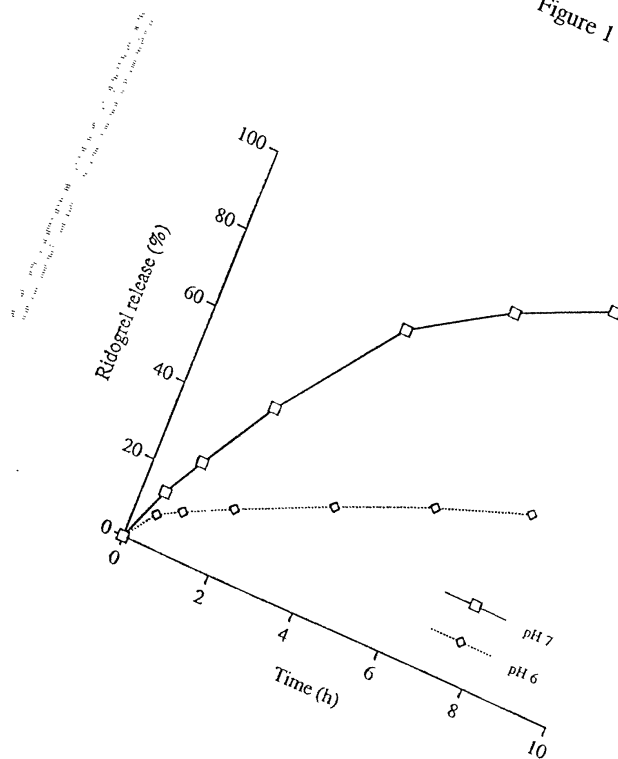
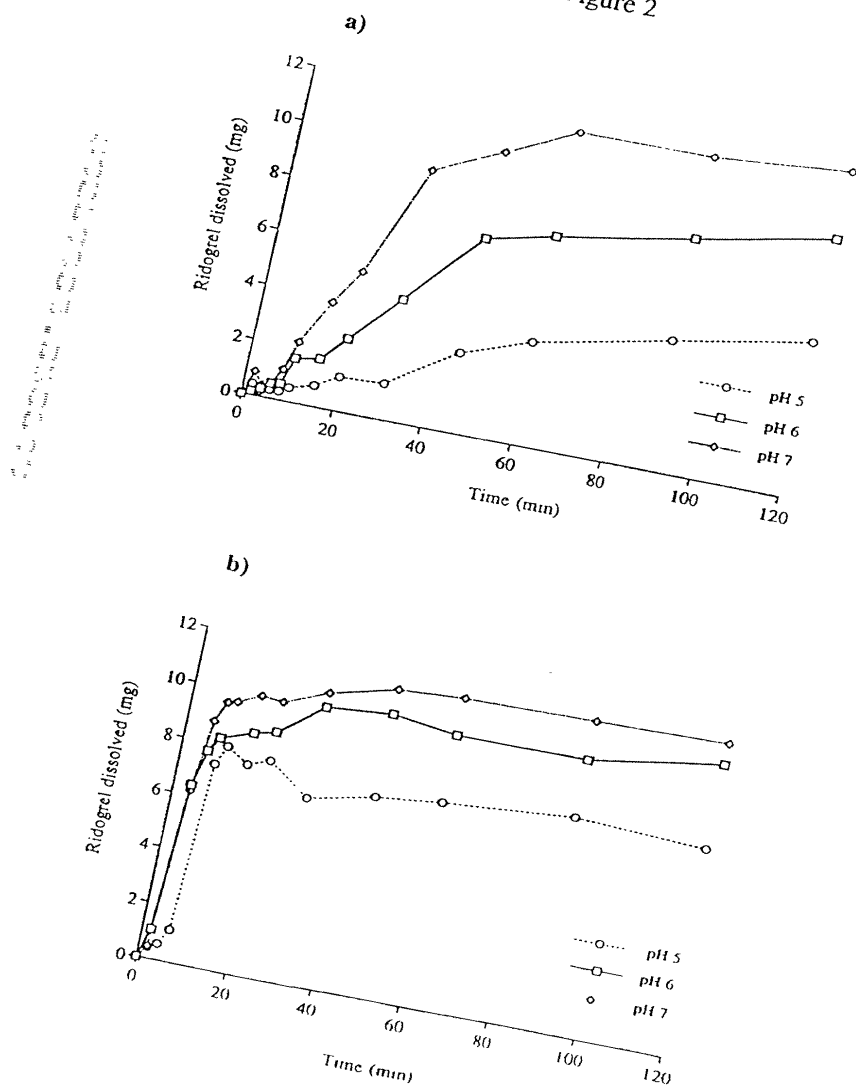


Figure 2



3/7

Figure 3

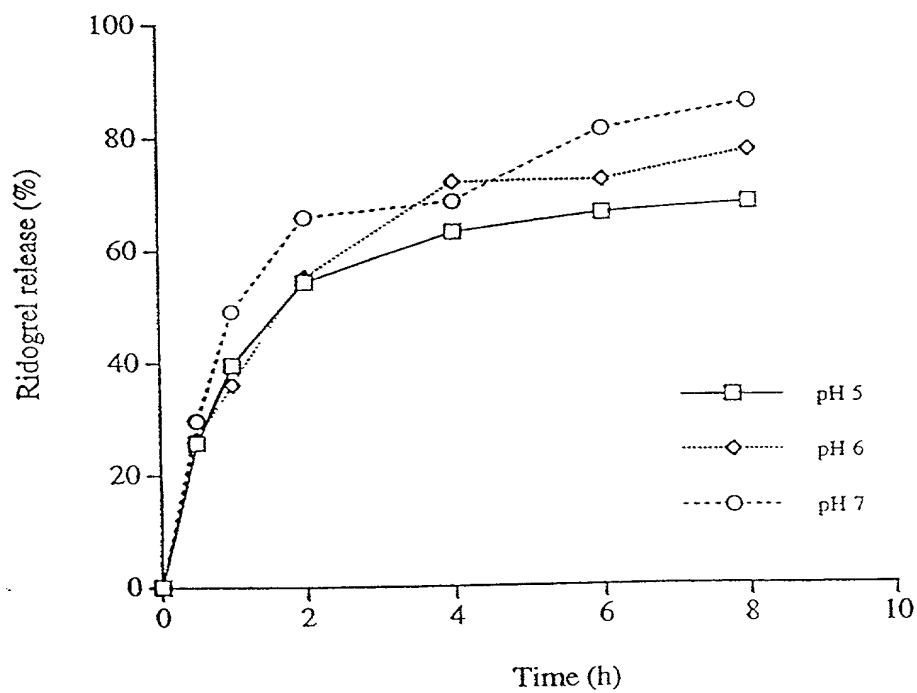
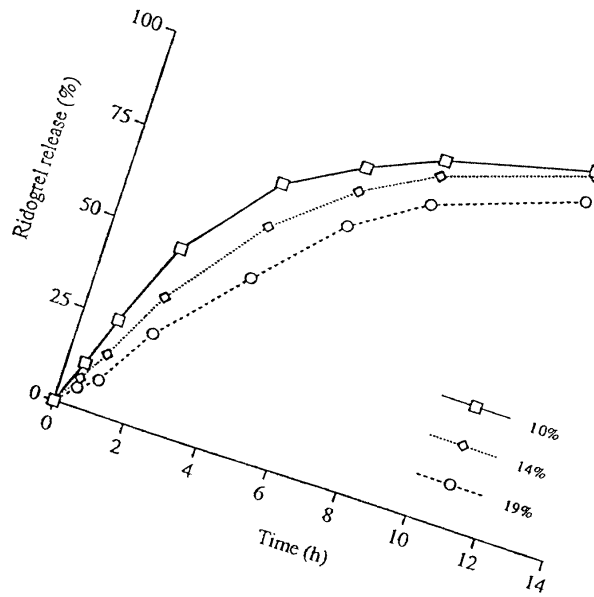
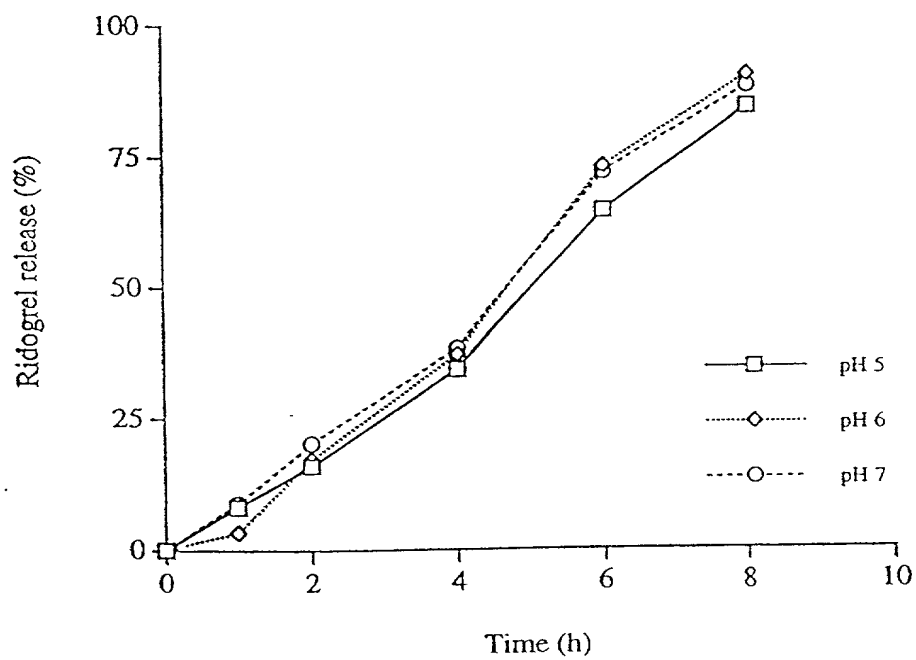


Figure 4



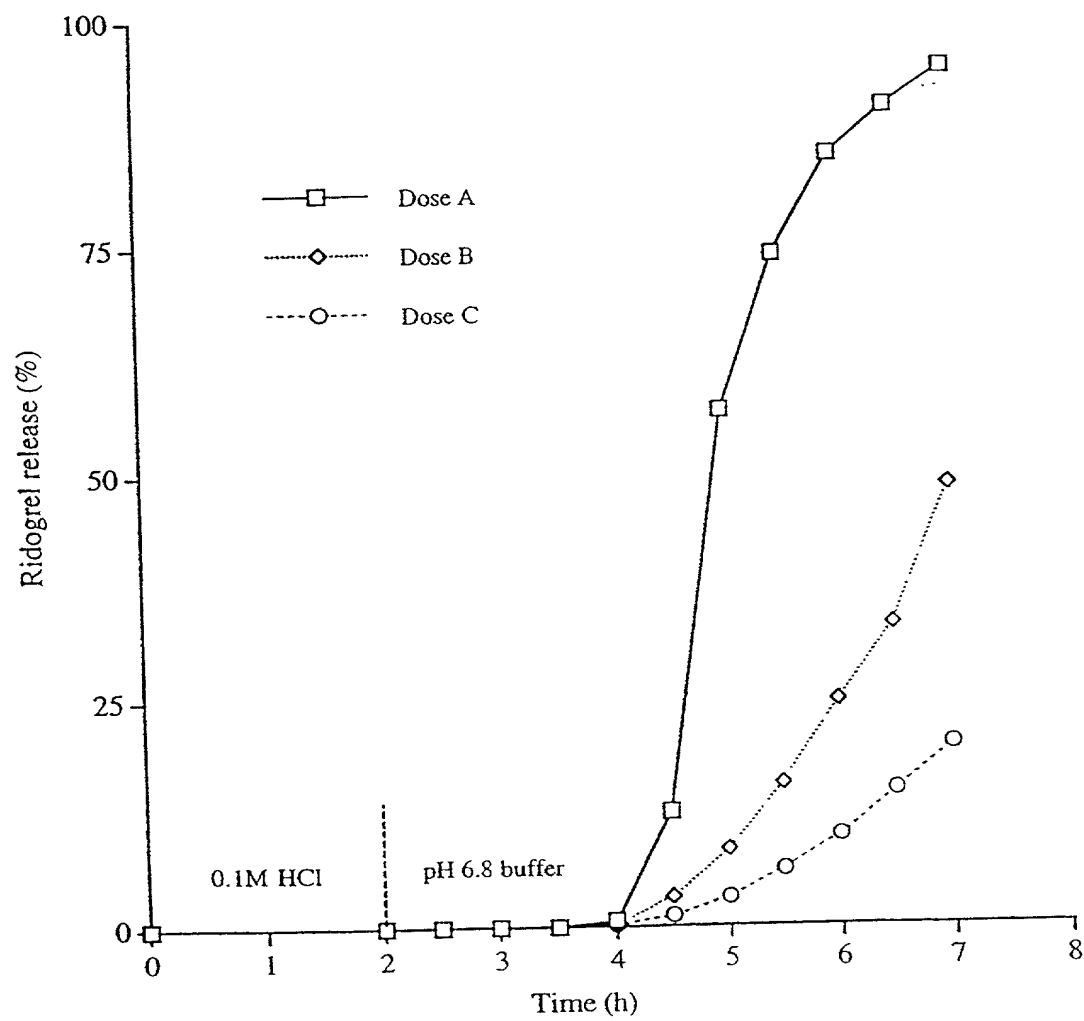
5/7

Figure 5



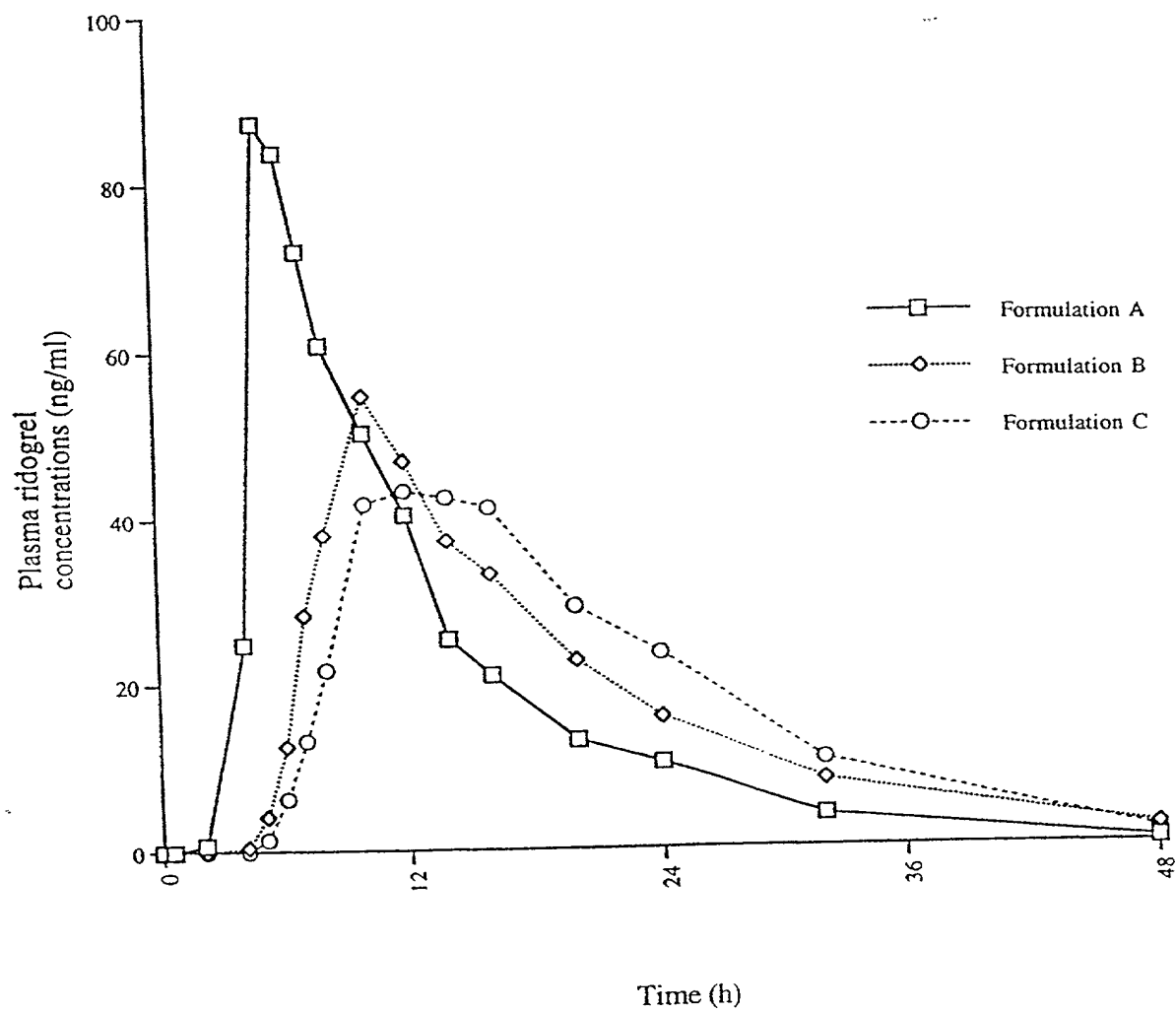
6/7

Figure 6



7/7

Figure 7



Please type a plus sign (+) inside this box → **+**

PTO/SB/01 (12-97)

Approved for use through 9/30/00. OMB 0651-0032  
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

<b>DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION</b> <b>(37 CFR 1.63)</b>  <input type="checkbox"/> Declaration Submitted with Initial Filing <input checked="" type="checkbox"/> Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)	<b>Attorney Docket Number</b>	WC 131
	<b>First Named Inventor</b>	Peter James Watts
	<b>COMPLETE IF KNOWN</b>	
	<b>Application Number</b>	09 / 269,903
	<b>Filing Date</b>	April 2, 1999
	<b>Group Art Unit</b>	
	<b>Examiner Name</b>	

**As a below named inventor, I hereby declare that:**

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**COLONIC DELIVERY OF WEAK ACID DRUGS**

the specification of which (Title of the Invention)

☐ is attached hereto  
OR  
☒ was filed on (MM/DD/YYYY) **10/06/1997** as United States Application Number or PCT International Application Number **PCT/GB97/02726** and was amended on (MM/DD/YYYY) (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
9620709.7	Great Britain	10/04/1996	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
PCT/GB97/02726	PCT	10/06/1997	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

[Page 1 of 2]

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231

WC 131

Please type a plus sign (+) inside this box → ☐

PTO/SB/01 (12-97)  
Approved for use through 9/30/00. OMB 0651-0032  
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

## DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

☐ Customer Number  OR

☒ Registered practitioner(s) name/registration number listed below

Place Customer  
Number Bar Code  
Label here

Name	Registration Number	Name	Registration Number
Patrea L. Pabst	31,284		
Robert A. Hodges	41,074		
Kevin W. King	42,737		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number  OR ☒ Correspondence address below

Name	Patrea L. Pabst		
Address	Arnall Golden & Gregory, LLP		
Address	2800 One Atlantic Center, 1201 West Peachtree Street		
City	Atlanta	State	GA
ZIP	30309-3450		
Country	United States	Telephone	(404)873-8794
Fax	(404)873-8795		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))		Family Name or Surname	
Peter James		Watts	
Inventor's Signature	P. J. Watts P. J. Watts		Date
Residence: City	Nottingham	State	GB
Post Office Address	Flat 2, 47 Highfield Road		
Post Office Address	West Bridgford		
City	Nottingham	State	GB
ZIP	NG2 6DR		
Country	GB		

☐ Additional inventors are being named on the supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto